INTERVIEW SUMMARY

The Examiner is thanked for the courtesies extended during a telephonic Interview conducted with the undersigned on January 25, 2008. During the interview, the rejections under 35 USC § 112, first paragraph, were discussed. The Examiner agreed to review these rejections in light of the arguments presented below. In an effort to further prosecution, a Declaration of Dr. Nigel J. Mouncey, who is a named co-inventor, is filed concurrently herewith confirming that the process claimed is fully enabled and that Applicants were in possession of the claimed invention at the time the application was filed. In view of the Declaration and the remarks below, withdrawal of the rejections and allowance of the claims are respectfully requested.

REMARKS

35 U.S.C. § 112, Second Paragraph, Rejection:

Claims 23 and 32 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. (Paper No. 20070803 at 12).

In making the rejection, the Examiner asserted that claims 23 and 32 are indefinite because of the term "mutation." (*Id.*). The Examiner further asserted that "[t]he term cited renders the claim indefinite" because "it is unclear where this mutation occurs." (*Id.*).

As is well settled, all that is required to comply with 35 U.S.C. § 112, second paragraph, is that the metes and bounds of what is claimed be determinable with a reasonable degree of precision and particularity. *Ex parte Wu*, 10 USPQ2d 2031, 2033 (BPAI 1989). Here, as of the filing date of the present application, the state of the art with respect to the term "mutation" was well developed. Accordingly, it is

submitted that the scope of claims 23 and 32 would have readily been ascertainable to one skilled in the art when the claims are read in light of the description portion of the specification and the state of the art as of the filing date of the present application. For this reason alone, the rejection cannot stand and should be withdrawn.

The Examiner appeared to express concern over "where th[e] mutation occurs." (Paper No. 20070803 at 12). The legal standard for definiteness, however, is whether a claim reasonably apprises those of skill in the art of its scope. *In re Warmerdam*, 31 USPQ 2d 1754, 1759 (Fed. Cir. 1994). Here, claims 23 and 32 meet that standard. The Examiner is placing great weight on the *breadth* of the claims, instead of the definiteness of the term "mutation." That is legal error because the breadth of the claims is not a proper basis of rejection under §112, second paragraph. *In re Miller*, 169 USPQ 597 (CCPA 1971); MPEP § 2713.04.

To reject a claim under the second paragraph of 35 U.S.C. § 112, it is incumbent on the examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims. *Wu*, 10 USPQ2d at 2033. This, the Examiner has not done. The Examiner has not made any factual determination that establishes that one of ordinary skill in the art would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims based upon the term "mutation" as used in claims 23 and 32.

In this regard, we note that generally a "mutation" is an alteration in the genomic sequence of a microorganism. Here, the specification specifically defines the term "mutation" on page 8, line 16 to page 9, line 2:

> As used herein the term "mutation" refers to an alteration in the genomic sequence of the microorganism, which may be introduced by any convenient means including, for example, chemical and UV mutagenesis, followed by screening or selection for a desired phenotype, construction of dysfunctional genes in vitro by recombinant techniques used to replace the intact counterparts of the genes in the genome of the microorganism, by single and double cross-over recombinations, and other well known techniques. See, Sambrook, et al., Molecular Cloning, A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press (1989) and, Harwood and Cutting, Molecular Biology Methods For Bacillus, John Wiley and Sons (1990), pp. 27-74. [Page 8, line 16 to page 9, line 2].

Nothing more is required. Indeed, the Board recently in *Ex parte Rollins*, 2003 WL 25281876, *3 (BPAI 2003) (unpublished) criticized an Examiner for making the very same rejection. There, the Board stated that:

> We ***do not agree*** that the claims are indefinite because they use ***the terms "mutation"***, "allelic variation", "hybridizes", "specifically hybridizes", and "stringent". ***As pointed out by Appellants, these terms are adequately defined in the specification*** (see, e.g., page 6 for exemplary stringent and non-stringent hybridization conditions, pages 7-8 for a discussion of JE mutations, and page 7, lines 1-3, for a definition of allelic variations). ***Thus, these terms would not have prevented those skilled in the art from understanding the scope of the claims.*** [Emphasis added].

Thus, the use of the term "mutation" is not *per se* indefinite. And merely characterizing the term as such does not satisfy the Examiner's burden. For this additional reason, the rejection cannot stand and should be withdrawn.

For the reasons set forth above, the rejection of claims 23 and 32 has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

§112, First Paragraph Rejections

1. Enablement

Claims 23-26 and 32 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. (Paper No. 20070803 at 2). In making the rejection, the Examiner concluded that the claims were not commensurate in scope with the specification, and, therefore, that it would require undue experimentation to practice the claimed invention. (*Id.* at 2-8). The crux of the rejection appears to lie with the Examiner's assertion that "the art does not disclose the mutation in the genes of the biotin biosynthesis that causes biotin auxotrphy" and that "there is no [ ] structure/activity correlation for the mutated polynucleotides involved in biotin biosynthesis [in the specification], and the number of possible mutations in the biotin biosynthesis genes to be tested is virtually endless." (*Id.* at 5 and 8).

The Examiner conceded, however, that the specification is enabling:

> for a process for decoupling production of a specific target fermentation product (i.e., riboflavin) from biomass production in a fermentation medium, the method comprising: (a) providing a recombinantly produced microorganism of bacillus that contains a polynucleotide sequence which encodes biosynthetic enzymes for the target fermentation product (i.e., riboflavin), (b) introducing a specific mutated polynucleotide sequence such as SEQ ID NO: 1 causing a biotin auxotrophy into the microorganism to control biomass production, and (c) supplying the medium with unlimited amount of substrates for producing the riboflavin and with a limited amount of biotin complementing the auxotrophy; and a microorganism made by the process, ..." (*Id.* at 2-3).

Claim 23 currently recites, *inter alia*, (1) that the recombinantly produced microorganism is a *Bacillus*, (2) that biotin is the specific auxotrophy, and (3) that riboflavin is the specific target fermentation product.

In an effort to further prosecution, we submit herewith a Declaration of Dr. Nigel J. Mouncey under 37 CFR § 1.132 ("Declaration"). Dr. Mouncey, who is a named co-inventor, demonstrates in the Declaration that the claimed process is fully enabled and that a person skilled in the art would readily be able to make and use the claimed invention.

In the Declaration, Dr. Mouncey discusses two articles that disclose the introduction of mutations into the biotin operon, which lead to, *e.g.*, biotin auxotrophs. (Declaration, ¶¶ 11-15). Dr. Mouncey identified Bower *et al.*, "Cloning, Sequencing, and Characterization of the *Bacillus subtilis* Biotin Biosynthetic Operon," J. Bact., Vol. 178, No. 14, pp. 4122-4130 (1996) ("Bower"), which discloses the construction of various *Bacillus subtilis* mutants which require biotin for their normal growth. (*Id.*, ¶¶ 11-13 and Figure 4 and Table 4). Bower further discloses the location of insertion and deletion mutations within the *Bacillus subtilis* bio operon. (*Id.*, ¶¶ 11-12).

Dr. Mouncey further identified Sasaki *et al.*, "Genetic Analysis of an Incomplete *bio* Operon in a Biotin Auxotrophic Strain of *Bacillus subtilis* Natto OK2," Biosci. Biotechnol. Biochem., Vol. 68, No. 3, pp. 739-742 (2004) ("Sasaki"), which discloses the introduction of auxotrophic mutants into the biotin operon. (*Id.*, ¶¶ 14-15). For example, Sasaki discloses a BioW gene mutation, which results in an opal stop codon and a deletion mutation in the BioF gene. (*Id.*).

And, as Dr. Mouncey stated, the genes involved in biotin biosynthesis were well known to those skilled in the art. (*Id.*, ¶¶ 15-16). In further support for the enablement of the claims, Dr. Mouncey reviewed the extensive disclosure in the specification. For example, Dr. Mouncey confirmed that the specification discloses that the mutation causing auxotrophic growth may be introduced using any convenient means, such as for example by "chemical and UV mutagenesis followed by screening or selection for a desired phenotype." (Specification, p. 8, lns. 16-19); (Declaration, ¶ 16).

Dr. Mouncey also confirmed that the specification discloses simple screens for confirming an auxotrophy:

> A microorganism that is an auxotroph for biotin is unable to grow without supplementation with biotin, *i.e.*, the substrate complementing the auxotroph. (*Id.*, p. 12, lns. 18-20).

Dr. Mouncey also confirmed that the specification provides specific exemplification of a process for decoupling production of riboflavin from biomass production with biotin auxotrophy is disclosed, including a description of how to make a specific biotin auxotroph. (*See*, *e.g.*, Specification, pp. 15-18; Examples 1-3; and Figs. 1-4); (Declaration, ¶ 16).

Dr. Mouncey stated that the level of knowledge and skill in this art is high (Declaration, ¶ 15). Indeed, the Examiner has confirmed this:

> The related art (references on pages 1-4 of the specification) teach recombinant production of riboflavin and genes involved in the riboflavin biosynthetic pathways; and the art (e.g., Bower et al. U.S. Patent 6,303,377) shows the genes of the biotin biosynthetic operon of *Bacllus subtitis*. (Paper No. 20070803 at 5).

In view of the extensive disclosures in the specification, the well characterized bio operon, including how to make biotin auxotrophs, and the high level of skill in the art, Dr. Mouncey concluded that once a motivation to make a biotin auxotroph was provided – to decouple production of target fermentation production from biomass production as disclosed in the present invention – it was well within the skill of the art to generate and screen for such mutants and that such work was routine and well within the skill of the art. (Declaration, ¶ 17).

Given Dr. Mouncey's unchallenged expert testimony regarding the scope of the disclosure of the present application, the detailed knowledge of one skilled in the art of the bio operon and how to make biotin auxotrophs, and the high level of skill in the art nothing more is required to satisfy the enablement requirements. Nonetheless, we note that even a "considerable amount" of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. MPEP § 2164.05 and *In re Wands*, 8 USPQ at 1404. As Dr. Mouncey's declaration clearly conveys, one skilled in the art, with the present application in hand would only be required to carry out routine experiments to make and identify other biotin auxotrophs. Accordingly, it is respectfully submitted that ample guidance is provided in the specification. Thus, for the reasons set forth above, the rejection should be withdrawn.

It is also well established that claims must be separately analyzed. *Ex parte Jochim*, 11 USPQ2d 561 (BPAI 1988). Here, the Examiner has not referred to any specific features of any of the dependent claims that are insufficiently enabled. To the contrary, the Examiner has yet again simply posited, in conclusory fashion, that, with respect to claim 23, "[t]he specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." (Paper No. 20070803 at 3). Accordingly, it is respectfully submitted, for this additional reason, that the rejection should be withdrawn as to claims 24-26.

In view of the foregoing and in light of Dr. Mouncey's Declaration, it is respectfully submitted that the rejection has been rendered moot and should be withdrawn.

2. Written Description

Claims 23-26 and 32 have been rejected under 35 U.S.C. §112, first paragraph. (Paper No. 20070803 at 8-12). In making the rejection, the Examiner asserted that claims 23-26 and 32 "contain[ ] subject matter which was not described in specification ...." (*Id.* at 8). The Examiner further asserted that "the specification does not disclose a genus of variants for mutated polynucleotides that cause biotin auxotrophy in a transformed microorganism." (*Id.* at 10). The Examiner then concluded that:

> While the genes involved in biotin biosynthesis are known in the art, a convenient means may be used to introduce a mutation in the genes involved in biotin biosynthesis, and a screening method may be used to confirm a biotin auxotrophy, the specification does not disclose the structure/activity correlation for the mutated polynucleotides, and the number of possible mutations in the biotin biosynthesis genes to be tested is virtually endless. (*Id.* at 11).

Claim 23 currently recites, *inter alia*, (1) that the recombinantly produced microorganism is a *Bacillus*, (2) that biotin is the specific auxotrophy, and (3) that riboflavin is the specific target fermentation product.

In an effort to further prosecution, the Declaration of Dr. Mouncey is submitted to demonstrate that the claimed process is described in the specification in such a way to reasonable convey to one skilled in the art that Applicants were in possession of the claimed invention as of the filing date.

As noted above, Dr. Mouncey identified two articles, Bower and Sasaki, that provide insight into the well developed nature of this particular field. And, Dr. Mouncey further highlighted the extensive disclosure in the present application.

For example, Dr. Mouncey noted that the present specification discloses how to make mutations that may lead to auxotrophs (*see, e.g.,* Specification, p. 8, lns. 16-19 and Declaration at ¶ 18), simple assays for confirming an auxotrophy (*Id.*, p. 12, lns. 18-20 and Declaration at ¶ 18), and exemplification of the specific biotin auxotroph (*see, e.g.*, Specification, pp. 15-18; Examples 1-3; and Figs. 1-4 and Declaration at ¶ 20). We also note that the Examiner has acknowledged the description, in the specification, of an exemplification of a biotin auxotroph, namely:

> [A] process for decoupling production of a target fermentation product from biomass production in a fermentation medium by introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO: 1 into *bacillus subtilis* RB50 containing multiple copies of the engineered *rib* operon pRF69, culturing fermentations, and measuring biomass and riboflavin production at different biotin concentrations, which shows the product yield (i.e., the amount of riboflavin produced on the consumed glucose) is 33% higher in the decoupled process to the coupled process (see Examples 1-3) .... (Paper No. 20070803 at 9-10).

We further note that Dr. Mouncey opined that given the level of skill in the art, the well known structure and organization of the biotin operon, including how to make and identify such auxotrophs, and the extensive disclosure in the specification

that there was "no need to identify structure/function correlations" in order to demonstrate possession of the claimed invention. As is well settled, there are instances where the disclosure of a single species is sufficient to put one skilled in this art in possession of a genus. *In re Rasmusson*, 211 USPQ 323, 326-27 (CCPA 1981). We respectfully submit that this is one of those instances, particularly in view of Dr. Mouncey's expert opinion, the well developed nature of the art, the level of skill in the art, and the extensive disclosure, including the examples of a working system within the scope of, *e.g.*, claim 23. (Declaration, ¶¶ 11-15).

Moreover, a proper written description analysis requires an analysis of the understanding of an ordinarily skilled artisan at the time of the invention. *See* MPEP § 2163(II)(A)(2); *see also Wang Labs. v. Toshiba Corp.*, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993). As noted above, the specification provides ample information on the structures of biotin auxotrophs and how to identify them. (*See, e.g.,* Specification at pages 11-18 and Examples 1-3); (Declaration, ¶¶ 18-21). And, the Examiner has conceded that the methods for making recombinant riboflavin were known, that the biosynthetic pathway of riboflavin was known, and how to make auxotrophs was known. In view of the foregoing, it is respectfully submitted that the Applicants were in possession of the full scope of the instantly claimed invention at the time the application was filed.

Accordingly, it is respectfully submitted that the rejection has been rendered moot and should be withdrawn.

For the reasons set forth above, entry of the Declaration of Dr. Nigel J. Mouncey under 37 CFR § 1.132, withdrawal of all rejections, and allowance of all

claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on February 7, 2008.

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